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Research Article

STUDIES ON ANTICONVULSANT ACTIVITY OF ANNACYCLUS PYRETHRUM IN ALBINO MICE

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ABSTRACT

Objective: A study which involves in detecting anticonvulsant activity from *Anacyclus pyrethrum* roots by using maximal electroshock seizure (MES) in a dose-dependent way with the production of ethanolic extraction.

Methods: The MES test is considered to be a predictor of likely therapeutic efficacy against generalized tonic-clonic seizures.

Results: MES-induced tonic seizures can be prevented either by drugs that inhibit voltage dependent Na^+ channels, such as phenytoin, valproate, and lamotrigine or by drugs that block glutamatergic excitation mediated by the N-methyl-D-aspartate receptor like felbamate.

Conclusion: The efficiency of *A. pyrethrum* will be detected after the incubation time of the animal, and the values of the ethanolic extraction will be tested for the anticonvulsant activity.

Keywords: *Anacyclus pyrethrum*, Albino mice, Maximal electroshock seizure, Anticonvulsant activity, Drugs.

INTRODUCTION

Anticonvulsant

Anticonvulsants (also commonly known as antiepileptic drugs [AEDs]) are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Failing this, an effective anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects, which may result in brain damage. Some studies have cited that anticonvulsants themselves are linked to lower IQ in children. However, these adverse effects must be balanced against the significant risk epileptiform seizures pose to children and the distinct possibility of death and devastating neurological secondary to seizures. Anticonvulsants are more accurately called AEDs, and are sometimes referred to as antiseizure drugs. While the term "anticonvulsant" is a fair description of AEDs, the use of this term tends to lead to confusion between epilepsy and non-epileptic convulsions. Convulsive non-epileptic seizures are quite common, and these types of seizures do not respond to AEDs. In epilepsy, an area of the cortex is typically hyper-irritable. This condition can often be confirmed by completing a diagnostic electroencephalogram (EEG). AEDs function to help reduce this area of irritability and thus prevent epileptiform seizures.

Conventional AEDs block sodium channels or enhance gamma-aminobutyric acid (GABA) function. Several AEDs have multiple or uncertain mechanisms of action. Next to the voltage-gated sodium channels and components of the GABA system, their targets include $GABA_A$ receptors, the GABA transporter-1, and GABA transaminase. Additional targets include voltage-gated calcium channels, SV2A, and α2δ. By blocking sodium or calcium channels, AEDs reduce the release of excitatory glutamate, whose release is considered to be elevated in epilepsy, but also that of GABA. This is probably a side effect or even the actual mechanism of action for some AEDs, since GABA can itself, directly or indirectly, act proconvulsively. Another potential target of AEDs is the peroxisome proliferator-activated receptor alpha. The drug class was the US's 5th-best-selling in 2007.

Some anticonvulsants have shown antiepileptogenic effects in animal models of epilepsy. That is, they either prevent the expected development of epilepsy or can halt or reverse the progression of epilepsy. However, no drug has been shown to prevent epileptogenesis (the development of epilepsy after an injury such as a head injury) in human trials.

History

The first anticonvulsant was bromide, suggested in 1857 by Charles Locock who used it to treat women with "hysterical epilepsy" (probably catamenial epilepsy). Bromides are effective against epilepsy, and also cause impotence, which is not related to its anti-epileptic effects. Bromide also suffered from the way it affected behavior, introducing the idea of the "epileptic personality" which was actually a result of medication. Phenobarbital was first used in 1912 for both its sedative and antiepileptic properties. By the 1930s, the development of animal models in epilepsy research led to the development of phenytoin by Tracy Putnam and Houston Merritt, which had the distinct advantage of treating epileptic seizures with less sedation. By 1948 The Wealth of India has initiated A Dictionary of Indian Raw Materials and Industrial Products. By the 1970s, a National Institutes of Health initiative, the Anticonvulsant Screening Program, headed by Kiffin Penry, served as a mechanism for drawing the interest and abilities of pharmaceutical companies in the development of new anticonvulsant medications. The guideline has been created by Veeraraghvan in the year of 2000. By 2002, Robert Bentley has explained briefly about the medicinal plant, followed by that the encyclopedia for the Indian medicinal plants was published by Berlin *et al*. in the year of 2007.

Drugs

In the following list, the dates in parentheses are the earliest approved use of the drug.

Aldehydes

- Paraldehyde (1882). One of the earliest anticonvulsants. It is still used to treat status epilepticus, particularly where there are no resuscitation facilities.

Aromatic allylic alcohols

- Stiripentol (2001 - limited availability). Indicated for the treatment of severe myoclonic epilepsy in infancy.

Barbiturates

Barbiturates are drugs that act as central nervous system (CNS) depressants, and by virtue of this they produce a wide spectrum of effects, from mild sedation to anesthesia. The following are classified as anticonvulsants:

- Phenobarbital (1912). See also the related drug primidone
- Methylphenobarbital (1935). Known as mephobarbital in the US. No longer marketed in the UK
- Barbexaclone (1982). Only available in some European countries.

Phenobarbital was the main anticonvulsant from 1912 till the development of phenytoin in 1938. Today, phenobarbital is rarely used to treat epilepsy in new patients since there are other effective drugs that are less sedating. Phenobarbital sodium injection can be used to stop acute convulsions or status epilepticus, but a benzodiazepine such as lorazepam, diazepam or midazolam is usually tried first. Other barbiturates only have an anticonvulsant effect at anesthetic doses.

Benzodiazepines
The benzodiazepines are class of drugs with hypnotic, anxiolytic, anticonvulsive, amnestic and muscle relaxant properties. Benzodiazepines act as a CNS depressant. The relative strength of each of these properties in any given benzodiazepine varies greatly and influences the indications for which it is prescribed. Long-term use can be problematic due to the development of tolerance to the anticonvulsant effects and dependency. Of the many drugs in this class, only a few are used to treat epilepsy:

In 1994 Wolfman *et al.* published the Possible anxiolytic effects of chrysin, a central benzodiazepine receptors ligand isolated from *Passiflora coeruiea* pharmacol and by 1985 File and Pellow was studied The effects of triazolobenzodiazepines in two animals test of anxiety and in the hole board.

- Clobazam (1979). Notably used on a short-term basis around menstruation in women with catamenial epilepsy
- Clonazepam (1974)
- Clorazepate (1972).

The following benzodiazepines are used to treat status epilepticus:

- Diazepam (1963). Can be given rectally by trained care-givers
- Midazolam (N/A). Increasingly being used as an alternative to diazepam. This water-soluble drug is squirted into the side of the mouth but not swallowed. It is rapidly absorbed by the buccal mucosa
- Lorazepam (1972). Given by injection in hospital.

Nitrazepam, temazepam, and especially nimetazepam are powerful anticonvulsant agents. However their use is rare due to an increased incidence of side-effects and strong sedative and motor-impairing properties.

Bromides

- Potassium bromide (1857). The earliest effective treatment for epilepsy. There would not be a better drug until phenobarbital in 1912. It is still used as an anticonvulsant for dogs and cats.

Carbamates

- Felbamate (1993). This effective anticonvulsant has had its usage severely restricted due to rare but life-threatening side effects.

Carboxamides

Carbamazepine

The following are carboxamides:

- Carbamazepine (1963). A popular anticonvulsant that is available in generic formulations
- Oxcarbazepine (1990). A derivative of carbamazepine that has similar efficacy, but is better tolerated and is also available generically
- Eslicarbazepine acetate (2009).

Fatty acids
The following are fatty acids:

- The valproates-valproic acid, sodium valproate, and divalproex sodium (1967)
- Vigabatrin (1989)
- Progabide
- Tiagabine (1996).

Vigabatrin and progabide are also analogs of GABA.

Fructose derivatives

- Topiramate (1995).

GABA analogs

- Gabapentin (1993)
- Pregabalin (2004).

Hydantoins
The following are hydantoins:

- Ethotoin (1957)
- Phenytoin (1938)
- Mephenytoin
- Fosphenytoin (1996).

Oxazolidinediones
The following are oxazolidinediones:

- Paramethadione
- Trimethadione (1946)
- Ethadione.

Propionates

- Beclamide.

Pyrimidinediones

- Primidone (1952).

Pyrrolidines

- Brivaracetam
- Levetiracetam (1999)
- Seletracetam.

Succinimides
The following are succinimides:

- Ethosuximide (1955)
- Phensuximide
- Mesuximide.

Sulfonamides

- Acetazolamide (1953)
- Sultiame
- Methazolamide
- Zonisamide (2000).

Triazines

- Lamotrigine (1990).

Ureas

- Pheneturide
- Phenacemide.

Valproylamides (amide derivatives of valproate)

- Valpromide
- Valnoctamide.

Other

- Perampanel.

Anticonvulsant side effects
Your doctor may want to take occasional blood tests to monitor your health while taking an anticonvulsant. Some anticonvulsants can cause liver or kidney damage or decrease the amount of platelets in your blood. Your blood needs platelets to clot.

Each anticonvulsant may have slightly different side-effects. Common side-effects include:

- Dizziness
- Drowsiness
- Fatigue
- Nausea
- Tremor
- Rash
- Weight gain.

Most of these side-effects lessen with time. Long-term effects vary from drug to drug. In general:

- Pregnant women should not take anticonvulsants without consulting with their doctor, because they may increase the risk of birth defects.
- Some anticonvulsants can cause problems with the liver over the long-term, so your doctor may monitor your liver closely.

Anticonvulsants can interact with other drugs – even aspirin - to cause serious problems. Be sure to tell your doctor about any drugs, herbs, or supplements you take. Don't take any other substance during treatment without talking with your doctor.

Anticonvulsants for chronic pain
Examples

Generic name	Brand name
Carbamazepine	Epitol, Tegretol
Gabapentin	Gralise, Neurontin
Oxcarbazepine	Trileptal
Pregabalin	Lyrica
Topiramate	Topamax

How it works

Experts do not know exactly how anticonvulsants work to reduce chronic pain. They may block the flow of pain signals from the CNS.

Why it is used

Anticonvulsant drugs typically are used to control seizures in people who have epilepsy. These drugs may also be used to treat other painful conditions, such as post-therpetic neuralgia and fibromyalgia.

How well it works

Some anticonvulsant drugs may work better than others for certain conditions. Anticonvulsants seem to work best when they are used for nerve pain. Examples of nerve pain include post-therpetic neuralgia and diabetic peripheral neuropathy.

About 7 out of 10 people with nerve pain who take carbamazepine have some relief from their pain, at least for a short time.

Gabapentin helps about 3-4 out of 10 people who take it for nerve pain.

Anticonvulsants can reduce some persistent low back pain.

Pregabalin helps between 3 and 5 out of 10 people who take it for nerve pain, especially postherpetic neuralgia, diabetic peripheral neuropathy, and fibromyalgia.

Gabapentin is sometimes used to treat chronic pelvic pain.

Carbamazepine and oxcarbazepine are used to treat chronic pain from trigeminal neuralgia (sudden facial pain). The best evidence is for carbamazepine, but oxcarbazepine probably works well too.

Anticonvulsant therapy
The mainstay of seizure treatment is anticonvulsant medication. The drug of choice depends on an accurate diagnosis of the epileptic syndrome, as a response to specific anticonvulsants varies among different syndromes. The difference in response probably reflects the different pathophysiologic mechanisms in the various types of seizure and the specific epileptic syndromes. By 1995, Subramaniam *et al.* did a pharmacological study of felbamate blocks the N-methyl-D-aspartate (NMDA) receptor and by 1978 Mahe *et al.* studied pharmacological properties of several indigenous plants on the nervous system.

Some anticonvulsants (e.g., lamotrigine, topiramate, valproic acid, zonisamide) have multiple mechanisms of action and some (e.g., phenytoin, carbamazepine, ethosuximide) have only 1 known mechanism of action. Anticonvulsants can be divided into large groups based on their mechanisms, as follows:

- Blockers of repetitive activation of the sodium channel: Phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topiramate
- Enhancers of slow inactivation of the sodium channel: Lacosamide, rufinamide
- $GABA_A$ receptor enhancers: Phenobarbital, benzodiazepines, clobazam
- NMDA receptor blockers: Felbamate
- Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor blockers: Perampanel, topiramate
- T-calcium channel blockers: Ethosuximide, valproate
- N- and L-calcium channel blockers: Lamotrigine, topiramate, zonisamide, valproate
- H-current modulators: Gabapentin, lamotrigine
- Blockers of unique binding sites: Gabapentin, levetiracetam
- Carbonic anhydrase inhibitors: Topiramate, zonisamide
- Neuronal potassium channel (KCNQ [Kv7]) opener: Ezogabine.

Anticonvulsants for specific seizure types
This section discusses the use of anticonvulsant agents for absence, tonic or atonic, myoclonic, and tonic-clonic seizures. A discussion of treatment for focal onset seizures, including refractory cases, also follows, with some findings from the Veterans Administration (VA) Cooperative Studies and Standard and New Antiepileptic Drugs (SANAD) trial. By 2003 Sayyah *et al*. experimented root extract against seizures.

Absence seizures
If only absence seizures are present, most neurologists treat them with ethosuximide. If absence seizures are present along with other seizure types (e.g. generalized tonic-clonic seizures, myoclonic seizures), the choices are valproic acid, lamotrigine, or topiramate. Do not use carbamazepine, gabapentin or tiagabine, because these drugs may exacerbate absence seizures. It is uncertain whether pregabalin, a medication related to gabapentin, may also exacerbate this type of seizure.

Investigators of a single, double-blind, randomized, controlled trial that compared the efficacy, tolerability, and neuropsychologic effects of ethosuximide, valproic acid, and lamotrigine in children with newly diagnosed childhood absence epilepsy concluded that ethosuximide was the drug of choice for this clinical scenario. Valproate was equally as effective as ethosuximide in newly diagnosed childhood absence epilepsy, but it was associated with more adverse effects.

Tonic or atonic, myoclonic, and tonic-clonic seizures
Tonic or atonic seizures are dramatic seizures. Patients with Lennox-Gastaut syndrome may have seizures, and this syndrome is best treated with broad-spectrum drugs (e.g. valproic acid, lamotrigine, topiramate) or felbamate as a last resort. Other treatment modalities include the use of vagal nerve stimulation (VNS). The US Food and Drug Administration (FDA) approved several new agents –rufinamide (Banzel) in 2008, clobazam (ONFI) in 2011, and extended-release topiramate (Trokendi XR) in 2013–as adjunctive therapies for seizures associated with Lennox–Gastaut syndrome.

Myoclonic seizures have a bimodal distribution. Infants with myoclonic epilepsies usually have a poor prognosis; however, in late childhood

and adolescence, the syndrome of juvenile myoclonic epilepsy (JME) is often the cause of myoclonic seizures. The seizures associated with JME are usually readily controlled with the appropriate broad-spectrum AED, but JME has a high recurrence rate of approximately 80-90% after discontinuation of anticonvulsants.

The best medications for JME and myoclonic seizures are valproic acid, lamotrigine, and topiramate. Levetiracetam is approved by the FDA for adjunctive therapy of JME; this is the first medication approved for this syndrome. Anecdotal evidence suggests that zonisamide might be helpful in JME. Note that if partial seizure medications, such as phenytoin and carbamazepine, are used to treat JME, these agents may not only be ineffective, but in certain cases they may exacerbate the seizures.

Primary generalized tonic-clonic seizures respond to valproic acid, topiramate, or lamotrigine. Levetiracetam gained FDA approval in 2007 as adjunctive therapy for these seizures.

Generalized and unclassified epilepsies

The SANAD trial investigators concluded that valproate should remain the drug of first choice for many patients with generalized and unclassified epilepsies, as it is better tolerated than topiramate and more efficacious than lamotrigine. However, in women of childbearing age, the known potential adverse effects of valproate during pregnancy (i.e., black box warnings of severe birth defects and impaired cognitive development) must be balanced against the benefits of seizure control. Levetiracetam and zonisamide were not included in SANAD, which tested only lamotrigine, topiramate, and valproate.

A 2014 study by Shallcross *et al*., however, indicated that while in utero exposure to the AED valproate is associated with language and motor development deficits in children, the same is not true for levetiracetam. In the study, valproate exposure resulted in children having lower scores on tests of comprehension, expressive language abilities, and motor skills compared with children exposed to levetiracetam. In fact, children exposed to levetiracetam did not differ from children unexposed to any AED on tests of thinking, movement, and language when tested at age 36-54 months.

Focal-onset seizures

In focal onset seizures, there are many AED choices with monotherapy indications including carbamazepine, lamotrigine, oxcarbazepine, and topiramate (see anticonvulsants in specific patient populations, below). Adjunctive therapy with levetiracetam, tiagabine, gabapentin, pregabalin, lacosamide, or ezogabine may be considered if the first or second monotherapy trial with first-line treatments fails. Discussing the adverse-effect profiles of anticonvulsants with patients is important, because the efficacies of anticonvulsants appear to be similar.

The VA Cooperative Study I clearly demonstrated similar efficacies for carbamazepine, phenytoin, primidone, and phenobarbital. However, carbamazepine and phenytoin were tolerated better by men than women. The VA Cooperative Study II findings showed that carbamazepine and valproic acid had similar efficacies. However, subset analysis for complex focal seizures suggested that carbamazepine may be a better choice than valproate.

In elderly subjects (patients aged ≥60 year) in the VA Cooperative Study, lamotrigine and gabapentin were better tolerated than carbamazepine and were similarly effective. However, gabapentin caused more adverse effects than lamotrigine. Those results led to the recommendation of lamotrigine as first-line monotherapy in elderly patients.

The focal seizures arm of the SANAD trial demonstrated that although carbamazepine is the standard drug treatment, lamotrigine is clinically better with respect to time to treatment failure. This study also determined that lamotrigine is a cost-effective alternative to carbamazepine for patients with focal onset seizures. Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, and topiramate were included for comparison. However, the cost-effectiveness of medications has changed, as many new AEDs also have generic formulations.

Of the new anticonvulsants, lamotrigine and topiramate appear to have broad spectrum of action in many seizure types. The American Academy of Neurology and the American Epilepsy Society assembled a task force that reviewed the literature and provided evidence-based recommendations for monotherapy, adjunctive therapy, treatment of primary generalized seizures, treatment in children, and treatment of subgroups of new-onset and refractory epilepsy.

If carbamazepine fails to control the seizures, lamotrigine, topiramate, tiagabine, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and zonisamide are considered for second- or third-line therapy. Several new anticonvulsants, including lamotrigine, topiramate, and oxcarbazepine, are indicated as monotherapy. Although the new anticonvulsants are considered second- or third-line therapy, they can be used as first-line therapy in some patients, especially as these medications have become generic.

Risk of seizure recurrence

Many neurologists use the risk factors for new-onset seizures to assess patients for discontinuation of anticonvulsants. Normal findings on an EEG and a brain magnetic resonance imaging (MRI) scan lower the risk of relapse after drug discontinuation, whereas epileptiform or focal abnormalities on an EEG and/or focal cortical or limbic abnormalities on a brain MRI scan significantly increase the relapse risk.

Additional factors associated with an increased risk of seizure recurrence after discontinuation includes the following:

- Several seizure types (e.g., worse if tonic or atonic seizures are present)
- High number and frequency of seizures
- Long duration of epilepsy before the seizures were controlled
- Short duration of seizure freedom.

Seizure relapse

About 75% of seizure relapses after medication discontinuation occur in the 1st year, and at least 50% of patients who have another seizure do so in the first 3 months. Therefore, advise patients to observe strict seizure precautions (including not driving) during tapering and for at least 3 months after discontinuation, depending on state laws. The need to drive is an impediment for some patients, who may opt to continue therapy for that reason.

Some authors recommend that all anticonvulsants, except primidone, phenobarbital, and benzodiazepines, be gradually discontinued over 6-10 weeks if they were used for a long period. Discontinue primidone, phenobarbital, and benzodiazepines over 10-16 weeks.

Nonpharmacologic management

A ketogenic or modified Atkins diet and VNS are nonpharmacologic methods for managing patients with seizures that are unresponsive to AEDs. The ketogenic diet is typically used in children. The FDA has approved VNS stimulation for adolescents and adults with refractory partial epilepsy, but clinical experience also suggests efficacy and safety in children and in patients with generalized epilepsies.

Ketogenic diet and modified Atkins diet

The ketogenic diet, which relies heavily on the use of fat, such as hydrogenated vegetable oil shortening (e.g., Crisco), has a role in the treatment of children with severe epilepsy. Support for the efficacy of these diets comes from large observational studies rather than from randomized, controlled trials.

Although this diet is unquestionably effective in some refractory cases of seizure, a ketogenic diet is difficult to maintain; less than 10% of patients continue the diet after a year. Furthermore, any small carbohydrate intake (e.g., lollypop, piece of candy) resets ketone

metabolism for 2 weeks, thereby eliminating antiseizure efficacy. Consequently, some authors do not consider using this treatment in teenagers or adults unless the patient's entire caloric intake is being delivered by means of a gastric tube.

Preliminary data have been published about improvement of seizure frequency following a modified Atkins (low-carbohydrate) diet that mimics the ketogenic diet but does not restrict protein, calories, and fluids. In small studies of children with intractable epilepsy, seizure reductions of more than 50% have been seen within 3 months in some children placed on this diet, particularly with carbohydrate limits of 10 g/day.

Preliminary studies of a modified Atkins diet have also been performed in adults. For example, Smith *et al*. found that this diet demonstrates modest efficacy as adjunctive therapy for some adults with medically resistant epilepsy, and it may also be helpful for weight loss but can pose financial and logistical difficulties.

VNS

VNS is a palliative technique that involves the surgical implantation of a stimulating device. VNS is FDA approved to treat medically refractory focal onset epilepsy in patients older than 12 years. Some studies demonstrate its efficacy in focal onset seizures and in a small number of patients with primary generalized epilepsy. Randomized studies showed modest efficacy at 3 months, but postmarketing experience showed delayed improvement in another group of patients.

Guidelines on vagus nerve stimulation for epilepsy

In August 2013, the American Academy of Neurology issued an update to its 1999 guidelines on the use of VNS for epilepsy. VNS is currently indicated for patients older than 12 years with medically intractable partial seizures who are not candidates for potentially curative surgical resections, as well as for the adjunctive long-term treatment of chronic or recurrent depression in patients older than 18 years with a major depressive episode not adequately relieved by 4 or more antidepressant treatments. Recent reports also indicate long-term efficacy and successful VNS use in pediatric epilepsy and other seizure types and syndromes.

Key recommendations of the updated guidelines include the following:

- VNS may be considered for (1) the adjunctive treatment of partial or generalized epilepsy in children, (2) seizures associated with Lennox-Gastaut syndrome, and (3) improving mood in adults with epilepsy
- VNS may have improved efficacy over time
- Children should be carefully monitored for site infection after VNS implantation.

According to the manufacturer's registry, efficacy of the stimulating device at 18 months is 40-50%, where efficacy is defined as a seizure reduction of 50% or more. Many patients report improvement in seizure intensity and general mood. However, seizure-free rates for pharmacologically intractable focal onset epilepsy are less than 10%.

A meta-analysis of VNS clinical studies reported an average reduction in seizures of at least 50% in approximately 50% of patients at last follow-up. Although VNS was not initially FDA approved for children or patients with generalized epilepsy, the authors also found that these groups benefitted significantly from VNS.

Positive predictors of a favorable outcome with VNS therapy include posttraumatic epilepsy and tuberous sclerosis. Few patients achieve complete seizure freedom with VNS, and about a quarter of patients receive no benefit in their seizure frequency. Some patients have clinical improvement in terms of milder and shorter seizures.

Implantable neurostimulator

The Neuro Pace RNS System, a device that is implanted into the cranium, senses and records electrocorticographic patterns and delivers short trains of current pulses to interrupt ictal discharges in the brain. The Neurological Devices panel of the FDA concluded that this device was safe and effective in patients with partial-onset epilepsy in whom other antiepileptic treatment approaches have failed and that the benefits outweigh the risks.

In November 2013, the FDA approved the Neuro Pace RNS System for the reduction of seizures in patients with drug-resistant epilepsy. Approval was based on a clinical trial involving 191 subjects with drug-resistant epilepsy. The neurostimulator was implanted in all of these patients but activated in only half of them. After 3 months, the average number of seizures per month in patients with the activated device fell by a median of 34%, compared with an approximately 19% median reduction in patients with an unactivated device.

Lobectomy and lesionectomy

The 2 major kinds of brain surgery for epilepsy are palliative and potentially curative. In the past, the most common palliative surgery was anterior callosotomy, which was indicated for patients with intractable atonic seizures, who often sustain facial and neck injuries from falls. This surgery is still performed as the use of VNS in such patients has good efficacy.

Several curative surgeries are possible, including lobectomy and lesionectomy. In general, the epileptogenic zone must be mapped by using video-EEG monitoring and, in some patients, with intracranial electrodes.

Lobectomy

Outcomes of temporal-lobe surgeries are better than those for surgeries in other areas. If a patient has unilateral temporal-lobe seizures (as observed on video-EEG) and unilateral hippocampal sclerosis (as observed on brain MRI), the likelihood of a class I outcome (no seizures or only auras) at 2 years is about 85%.

In a randomized, controlled trial of surgery in 80 patients with temporal lobe epilepsy, 58% of patients in the group randomized to anterior temporal lobe resective surgery were free from seizures impairing awareness at 1-year, as compared with 8% in the group that received anticonvulsant treatment. Quality of life was also superior for patients in the surgical group.

According to research, MRI-guided selective laser amygdalohipp ocampectomy (SLAH) is at least as effective as standard resection. In a study of 7 patients who received SLAH and 10 patients who underwent standard resection (either open anterior temporal lobectomy or selective amygdalohippocampectomy), 9 of 10 patients in the latter group showed a significant decline on visual/verbal memory tasks ($p<0.002$), compared with 1 of 7 patients in the former group. Whereas 6 of 7 laser-ablation patients showed significant improvement on 1 or more memory measures, only 4 of 10 standard-resection patients did ($p<0.02$).

Lesionectomy

In a study presented at the 66th Annual Meeting of the American Epilepsy Society, investigators suggested that, in select pediatric patients, smaller lesionectomy resections in the surgical treatment of seizures may be as effective as larger resections, and they may spare children the functional and developmental deficits associated with the larger resections.

The researchers reported on the outcomes of 25 children with MRI-negative, intractable partial epilepsy who underwent focal corticectomies. Epileptogenic regions were identified by three-dimensional EEG, single-photon emission computed tomography scanning, positron emission tomography scanning, and invasive EEG data. Seizure-free outcomes occurred in 3 of 7 patients with Type I focal cortical dysplasia, 7 of 12 patients with Type II focal cortical dysplasia, and 3 of 6 patients with mild malformations of cortical development.

Surgery for drug-resistant epilepsy

Although surgery for drug-resistant epilepsy is often considered a last resort, results of a multicenter trial suggested that early surgery may be helpful in some patients with newly intractable and disabling temporal lobe epilepsy. In this trial, patients who had had no more than 2 consecutive years of disabling seizures refractory to adequate trials of 2 anticonvulsant medications were randomized to anteromesial temporal lobe resection plus continued medication (n=15) or continued medication alone (n=23).

At follow-up, 11 of the 15 surgery patients (73%) were seizure free during postoperative year 2; none of the patients in the medication-only group were seizure free over the same period. The researchers warned, however, that the results must be interpreted cautiously, as the trial was halted prematurely because of slow accrual. In reference of this by 1990 Rogawski *et al.* and in 1995 Macdonald has discussed about the mechanism of the drug and compounds.

Activity modification and restrictions

The major problem for patients with seizures is the unpredictability of the next seizure. Clinicians should discuss the following types of seizure precautions with patients who have epileptic seizures or other spells of sudden-onset seizures:

- Driving
- Ascending heights
- Working with fire or cooking
- Using power tools or other dangerous equipment
- Taking unsupervised baths
- Swimming.

These lifestyle precautions are clearly more applicable to some patients than to others. Document on the patient's chart that driving and occupational hazards for people with seizures were discussed.

Safety must be balanced with the risk for seizures. A patient with many poorly controlled diurnal seizures may exercise more caution than a patient who has only nocturnal seizures. Encourage the use of helmets to prevent head trauma while the patient is biking, skiing, or participating in other high-risk activities.

Driving motorized vehicles

Driving restrictions differ for each patient because of the individual features of their seizures, their degree of seizure control, and, in the United States, state laws. US physicians should be aware of the state regulations regarding driving, which vary considerably among states. If clinicians practice in a state that requires mandatory reporting of patients with epilepsy to the Department of Motor Vehicles, they must ensure they are compliant with state laws and have documentation. International variation regarding reporting is also considerable; some countries have more permissive or more restrictive laws regarding driving than do the United States.

Aside from state laws, recommendations regarding driving motorized vehicles also vary depending on whether the patient has seizures that occur exclusively during sleep. Consult current state and federal laws and regulations. For example, to resume commercial driving across state lines, a patient must have a 5 years seizure-free period. The recommendation for driving cars and trucks extends to the operation of other motorized vehicles, such as boats and motorcycles. Aircraft pilots are typically no longer permitted to fly.

Water precautions

Common sense dictates that patients with seizures should not swim alone, and they should be particularly aware of the importance of the presence of an adult lifeguard who can pull them out of the water if needed. Wearing a life jacket in a boat is important. Activities as simple as taking a bath may be risky, because a person can drown in as little as 1 inch of water during the flaccid postictal phase. In addition, a patient who has a seizure while waiting for the bath water to warm up may suffer hot-water burns. The same experiment was performed by Bendjeddou *et al*. Immunostimulating activity of the hot water soluble polysaccharide extracts of *Anacyclus pyrethrum*, *Alpiniagalanga* and *Citrullus colocynthis* in 2003.

Heights, fire, and power tools

Patients with seizures may experience an episode in situations such as being up on a roof or engaging in some activity at a considerable height from the floor. In addition, burns from injuries related to cooking are not uncommon, and injuries can occur with the use of power tools and other dangerous equipment. Caution–in particular, supervision–is advised when power tools are used, and the use of safety devices, such as an automatic shut-off switch, is recommended.

Muscle relaxant

A muscle relaxant is a drug, which affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia. The term "muscle relaxant" is used to refer to two major therapeutic groups: Neuromuscular Blockers and spasmolytics. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no CNS activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause temporary paralysis. Spasmolytics, also known as "centrally acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions. While both neuromuscular blockers and spasmolytics are often grouped together as muscle relaxants, the term is commonly used to refer to spasmolytics only.

History

The earliest known use of muscle relaxant drugs dates back to the 16th century, when European explorers encountered natives of the Amazon Basin in South America using poison-tipped arrows that produced death by skeletal muscle paralysis. This poison, known today as curare, led to some of the earliest scientific studies in pharmacology. Its active ingredient, tubocurarine, as well as many synthetic derivatives, played a significant role in scientific experiments to determine the function of acetylcholine in neuromuscular transmission. By 1943, neuromuscular blocking drugs became established as muscle relaxants in the practice of anesthesia and surgery.

The U.S. FDA approved the use of carisoprodol in 1959, metaxalone in August, 1962, and cyclobenzaprine in August, 1977.

Neuromuscular blockers

Muscle relaxation and paralysis can theoretically occur by interrupting function at several sites, including the CNS, myelinated somatic nerves, unmyelinated motor nerve terminals, nicotinic acetylcholine receptors, the motor end plate, and the muscle membrane or contractile apparatus. Most neuromuscular blockers function by blocking transmission at the end plate of the neuromuscular junction. Normally, a nerve impulse arrives at the motor nerve terminal, initiating an influx of calcium ions, which causes the exocytosis of synaptic vesicles containing acetylcholine. Acetylcholine then diffuses across the synaptic cleft. It may be hydrolyzed by acetylcholine esterase or bind to the nicotinic receptors located on the motor end plate. The binding of two acetylcholine molecules results in a conformational change in the receptor that opens the sodium-potassium channel of the nicotinic receptor. This allows Na^+ and Ca^{2+} ions to enter the cell and K^+ ions to leave the cell, causing a depolarization of the end plate, resulting in muscle contraction. Following depolarization, the acetylcholine molecules are then removed from the end plate region and enzymatically hydrolyzed by acetylcholinesterase. Depressants of the CNS Screening procedure in Pharmacology have published in 1972.

Spasmolytics

The generations of the neuronal signals in motor neurons that cause muscle contractions are dependent on the balance of synaptic excitation

and inhibition the motor neuron receives. Spasmolytic agents generally work by either enhancing the level of inhibition or reducing the level of excitation. Inhibition is enhanced by mimicking or enhancing the actions of endogenous inhibitory substances, such as GABA.

Terminology

Because they may act at the level of the cortex, brain stem or spinal cord, or all three areas, they have traditionally been referred to as "centrally acting" muscle relaxants. However, it is now known not every agent in this class has CNS activity (e.g., dantrolene), so this name is inaccurate.

Most sources still use the term "centrally acting muscle relaxant." According to MeSH, dantrolene is usually classified as a centrally acting muscle relaxant. The World Health Organization, in its ATC, uses the term "centrally acting agents," but adds a distinct category of "directly acting agents," for dantrolene. Use of this terminology dates back to at least 1973.

The term "spasmolytic" is also considered a synonym for antispasmodic.

Clinical uses

Spasmolytics such as carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol are commonly prescribed for lowback pain or neck pain, fibromyalgia, tension headaches and myofascial pain syndrome. However, they are not recommended as first-line agents; in acute low back pain, they are not more effective than paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), and in fibromyalgia they are not more effective than antidepressants. Nevertheless, some (low-quality) evidence suggests muscle relaxants can add benefit to treatment with NSAIDs. In general, no high-quality evidence supports their use. No drug has been shown to be better than another, and all of them have adverse effects, particularly dizziness and drowsiness. Concerns about possible abuse and interaction with other drugs, especially if increased sedation is a risk, further limit their use. A muscle relaxant is chosen based on its adverse-effect profile, tolerability, and cost.

Muscle relaxants are thought to be useful in painful disorders based on the theory that pain induces spasm and spasm causes pain. However, considerable evidence contradicts this theory.

In general, muscle relaxants are not approved by FDA for long-term use. However, rheumatologists often prescribe cyclobenzaprine nightly on a daily basis to increase stage 4 sleep. By increasing this sleep stage, patients feel more refreshed in the morning. Improving sleep is also beneficial for patients who have fibromyalgia.

Muscle relaxants such as tizanidine are prescribed in the treatment of tension headaches.

Diazepam and carisoprodol are not recommended for older adults, pregnant women, or people who suffer depression or for those with a history of drug or alcohol addiction.

Mechanism

Because of the enhancement of inhibition in the CNS, most spasmolytic agents have the side-effects of sedation, drowsiness and may cause dependence with long-term use. Several of these agents also have abuse potential, and their prescription is strictly controlled.

The benzodiazepines, such as diazepam, interact with the $GABA_A$ receptor in the CNS. While it can be used in patients with muscle spasm of almost any origin, it produces sedation in most individuals at the doses required to reduce muscle tone.

Baclofen is considered to be at least as effective as diazepam in reducing spasticity and causes much less sedation. It acts as a GABA agonist at $GABA_B$ receptors in the brain and spinal cord, resulting in hyperpolarization of neurons expressing this receptor, most likely due to increased potassium ion conductance. Baclofen also inhibits neural function presynaptically, by reducing calcium ion influx, and thereby reducing the release of excitatory neurotransmitters in both the brain and spinal cord. It may also reduce pain in patients by inhibiting the release of substance P in the spinal cord, as well.

Clonidine and other imidazoline compounds have also been shown to reduce muscle spasms by their CNS activity. Tizanidine is perhaps the most thoroughly studied clonidine analog, and is an agonist at α_2-adrenergic receptors, but reduces spasticity at doses that result in significantly less hypotension than clonidine. Neurophysiologic studies show that it depresses excitatory feedback from muscles that would normally increase muscle tone, therefore minimizing spasticity. Furthermore, several clinical trials indicate that tizanidine has a similar efficacy to other spasmolytic agents, such as diazepam and baclofen, with a different spectrum of adverse effects.

The hydantoin derivative dantrolene is a spasmolytic agent with a unique mechanism of action outside of the CNS. It reduces skeletal muscle strength by inhibiting the excitation-contraction coupling in the muscle fiber. In normal muscle contraction, calcium is released from the sarcoplasmic reticulum through the ryanodine receptor channel, which causes the tension-generating interaction of actin and myosin. Dantrolene interferes with the release of calcium by binding to the ryanodine receptor and blocking the endogenous ligand ryanodine by competitive inhibition. Muscle that contracts more rapidly is more sensitive to dantrolene than muscle that contracts slowly, although cardiac muscle and smooth muscle are depressed only slightly, most likely because the release of calcium by their sarcoplasmic reticulum involves a slightly different process. Major adverse effects of dantrolene include general muscle weakness, sedation, and occasionally hepatitis.

Other common spasmolytic agents

Methocarbamol, carisoprodol, chlorzoxazone, cyclobenzaprine, gabapentin, metaxalone, and orphenadrine.

Side-effects

Muscle relaxants are very powerful drugs which may produce negative effects, including heart failure and paralysis. Patients most commonly report sedation as the main adverse effect of muscle relaxants. Usually, people become less alert when they are under the effects of muscle relaxant drugs. People are normally advised to not drive vehicles or operate heavy machinery while under muscle relaxants' effects.

Cyclobenzaprine produces confusion and lethargy, as well as anticholinergic side-effects. When taken in excess or in combination with other substances, it may also be toxic. While the body adjusts to this medication, it is possible for patients to experience dry mouth, fatigue, lightheadedness, constipation or blurred vision. Some serious but unlikely side-effects may be experienced, including mental or mood changes, possible confusion and hallucinations, and difficulty urinating. In a very few cases, very serious, but rare side effects may be experienced: irregular heartbeat, yellowing of eyes or skin, fainting, abdominal pain including stomachache, nausea or vomiting, lack of appetite, seizures, dark urine, or loss of coordination.

Patients taking carisoprodol for a prolonged time have reported dependence, withdrawal and abuse, although most of these cases were reported by patients who had had a history of addiction. These effects were also reported by patients who took it in combination with other drugs with abuse potential, and in fewer cases, there were reports of carisoprodol-associated abuse when used without other drugs with abuse potential.

Common side-effects eventually caused by metaxalone include dizziness, headache, drowsiness, nausea, irritability, nervousness, upset stomach and vomiting. Severe side effects may be experienced when consuming metaxalone, such as severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue), chills, fever, and sore throat, may require

medical attention. Other severe side effects include unusual or severe tiredness or weakness, as well as yellowing of the skin or the eyes. When baclofen is administered intrathecally, it may cause CNS depression accompanied with cardiovascular collapse and respiratory failure. Tizanidine may lower blood pressure. This effect can be controlled by administering a low dose at the beginning and increasing it gradually.

MATERIALS AND METHODS

Plant collection

- Collection of drugs
- Collection of the plant
- Literature survey
- Extraction of particular part of the plant by using soxhlet apparatus
- Collection of animals
- Note body weight of animals regularly
- Grouping of animals
- Maintained diet and water *ad libitium*
- Investigate the anticonvulsant and muscle relaxant activity by using different screening model
- Statistical analysis of the results.

Preparation of the extracts

The roots of *A. pyrethrum* were dried in air, crushed in coarse powder and subjected to successive extraction using ethanol in a soxhlet apparatus. The extract was concentrated under reduced pressure using rotatory evaporator at a temperature not exceeding 40°C and then dried in vacuum oven. The extract was stored in desiccators at a cool place and reconstituted in water for injection just before use.

Animals

Male albino mice (20-30 g) of either sex were procured from Sainath Agencies were housed in standard cages with free access of food (standard laboratory rodent's chow) and water. The animal house temperature was maintained at 23±3.0°C with a 12 hrs light/dark cycle. The Institutional Animal Ethics Committee approved the protocol of the study.

Drugs used

Phenytoin (Samarth Life Sciences Pvt. Ltd., Baddi, H.P., India) and Diazepam (Helios Pharmaceutical Pvt. Ltd., Baddi, H.P., India) were used in this study. The plant extract was dissolved in normal saline and subjected for anticonvulsant activity and muscle relaxant activity using maximal electroshock seizure (MES) and Rota rod models respectively. Phenytoin and Diazepam were dissolved in normal saline (0.9% NaCl solution).

Acute toxicity study

The acute toxicity for the ethanolic extract of roots of *A. pyrethrum* was determined in female albino mice (20-25 g). The animals were fasted overnight prior to the experiment and fixed dose OECD guideline No.420 (Annexure 2d) method of CPCSEA was adopted for acute toxicity studies. The ethanolic extract was administered in doses of 300, 2000, 5000 mg/kg. p.o., to group of mice, each containing ten animals and mortality was observed after 24 hrs.

Evaluation of anticonvulsant activity Maximum electroshock-induced seizures

Electro-convulsive shock, inducing Hind Limb Tonic Extension (HLTE) in 99% of the animals, was previously determined. Corneal electrodes were used for bilateral delivery of the electrical stimulus. Electro-convulsive shock (50 mA for 0.2 seconds.) was delivered through the corneal electrode to induce HLTE phase in mice. The electrical stimulus was applied using a stimulator apparatus for five groups of six each. Sayyah *et al.* performed the same technique for the detecting the anticonvulsant activity of the leaf in 2000.

Group I served as control (vehicle treated, i.p.);
Group II served as standard (received phenytoin sodium 25 mg/kg body weight, i.p.),
Group III, Group IV and Group V was treated with ethanolic extract as 200, 400 and 600 mg/kg body weight, i.p. respectively. The current was delivered after 30 minutes. of intraperitoneal administration of control and standard. The incidence and duration of HLTE was noted.

Myorelaxation activity Rota rod performance

The effect on motor co-ordination was assessed using Rotarod apparatus (Biocraft Scientific System Pvt. Ltd., Agra, India) Pre-selected mice (animal that stayed for at least 2 minutes. on the rotating bar, 24 hrs. before testing) were placed on the horizontal rotating bar (diameter 2.5 cm, 12 r.p.m.). The test was conducted on five groups of 6 mice each, 30 minutes after the administration of ethanolic extract (200, 400 and 600 mg/kg i.p.) and diazepam (1 mg/kg i.p.) and normal saline (10 ml/kg, i.p.).

Statistical analysis

The data was presented as mean ± standard error of mean. The data were analyzed by one-way analysis of variance, followed by Tukey multiple comparisons test. A difference of $p<0.001$ was considered significant in all cases.

RESULTS

Acute toxicity

In the acute toxicity study, the ethanolic extract of *A. pyrethrum* was found to be safe in the doses used and there was no mortality in a dose of 2 g/kg, i.p.

Evaluation of anticonvulsant activity Maximum electroshock-induced seizures

The ethanolic extract of *A. pyrethrum* exhibited almost dose dependent anticonvulsant activity. The extract significantly decreased the duration of HLTE phase in MES-induced seizures. The result is shown in Table 1.

Myorelaxation activity Rota rod performance

A significant dose dependent muscle relaxant effect of *A. pyrethrum* was observed in rotarod appararus compared to that produced by diazepam. The result is shown in Table 2.

Table 1: Effect of *A. pyrethrum* extract on MES induced seizures in mice

Serial number	Treatment	Duration of HLTE	Mortality (%)	Recovery (%)
1	Vehicle	15.63±0.52	80	-
2	Phenytoin	3.74±0.07	0	100
3	APE-200	11.94±0.58	0	71.47
4	APE-400	10.50±0.17	40	63.27
5	APE-600	7.45±0.63	0	55.08

APE-200, APE-400 and APE-600: *A. pyrethrum* extract dose 200, 400 and 600 mg/kg body weight. Values are mean±SEM, n=6, ***p<0.001 compared with control. SEM: Standard error of mean, MES: Maximal electroshock seizure, *A. pyrethrum*: *Anacyclus pyrethrum*

Table 2: Effect of ethanolic extract of *A. pyrethrum* on Rota rod test in mice

Serial number	Treatment	Time of fall (Seconds)	Mortality (%)
1	Vehicle	285±2.208	-
2	Diazepam	17.5±1.20	100
3	APE-200	195.48±4.29	90.82
4	APE-400	144.85±2.82	85.15
5	APE-600	83.92±1.92	77.82

Values are mean±SEM mice were pretreated with vehicle and APE i.p. 30 minutes before Rota rod model. ***p<0.001 (n=5). APE-200, APE-400 and APE-600: *A. pyrethrum* extract dose 200, 400 and 600 mg/kg body weight. SEM: Standard error of mean, MES: Maximal electroshock seizure, *A. pyrethrum: Anacyclus pyrethrum*

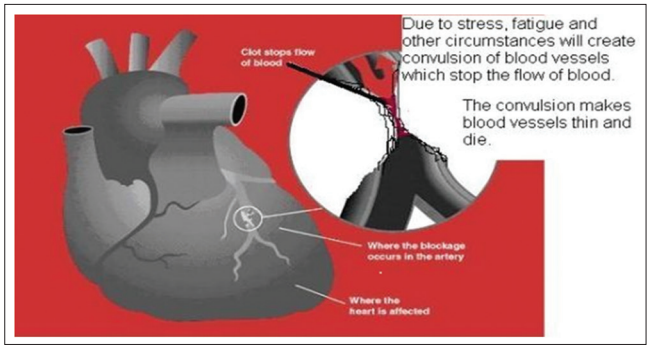

Fig. 1: Convulsion makes blood vessels thin and die

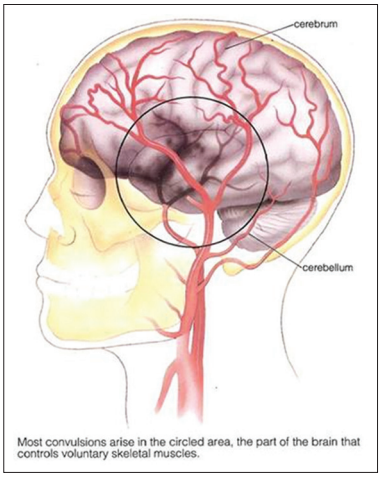

Fig. 2: Convulsions arise in the brain

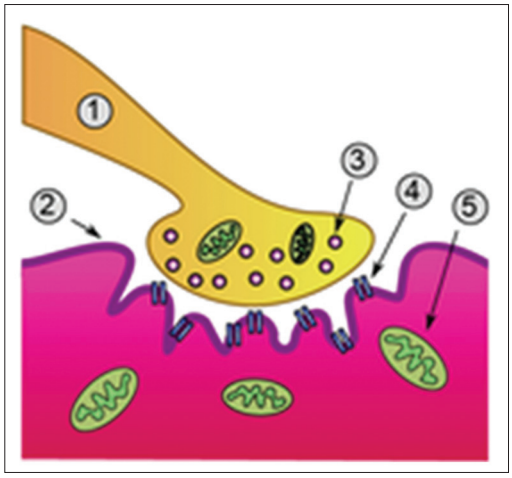

Fig. 3: Detailed view of a neuromuscular junction (1) presynaptic terminal (2) sarcolemma (3) synaptic vesicle (4) nicotinic acetylcholine receptor (5) mitochondrion

DISCUSSIONS

The observation emanated in the present study indicated that the *A. pyrethrum* was without any lethal effect in a dose up to 2 g/kg and possessed anticonvulsant activity against seizures induced by MES in a dose-dependent way. The most popular and widely used animal seizures model is the traditional MES test. The MES test is considered to be a predictor of likely therapeutic efficacy against generalized tonic-clonic seizures. MES-induced tonic seizures can be prevented either by

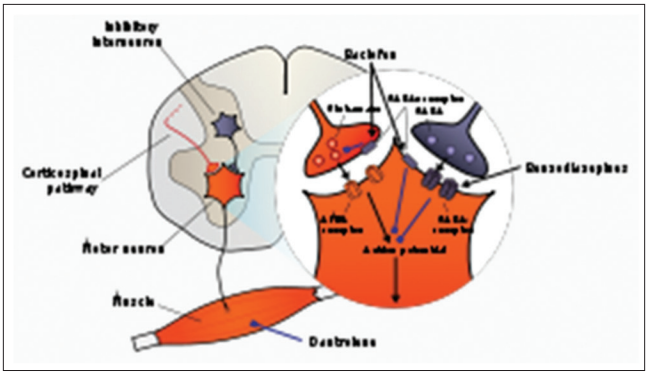

Fig. 4: A view of the spinal cord and skeletal muscle showing the action of various muscle relaxants – black lines ending in arrow heads represent chemicals or actions that enhance the target of the lines, blue lines ending in squares represent chemicals or actions that inhibition the target of the line

drugs that inhibit voltage dependent Na^+ channels, such as phenytoin, valproate and lamotrigine or by drugs that block glutamatergic excitation mediated by the NMDA receptor such as felbamate. The study showed that ethanolic extract from roots of *A. pyrethrum* can inhibit voltage dependent Na^+ channels as phenytoin in MES induced tonic seizures.

CONCLUSION

Thus, in conclusion, *A. pyrethrum* possesses anticonvulsant activity against the MES induced seizures. Further research is in progress to isolate the compound responsible for the activity.

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